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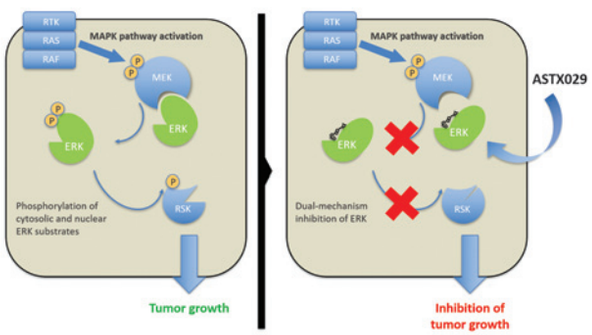
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

ASTX029 is a Dual-mechanism Inhibitor of ERK



Munck *et al.* | Page 1757

Relapse to MAPK pathway inhibitors (such as BRAF, MEK, and KRAS inhibitors) is common due to the reactivation of ERK and MAPK signaling. In this First Disclosure, Wallis, Munck, and colleagues outline the ERK inhibitor ASTX029. ASTX029 inhibits both the phosphorylation of ERK by MEK as well as its catalytic activity and, therefore, is categorized as a dual-mechanism inhibitor by the authors. The dual-mechanism ERK inhibitor demonstrated anti-tumor activity to MAPK inhibitor-resistant cancers in vitro and in vivo. Their work supports the continued clinical development of ASTX029 in advanced solid tumors.

Molecular Dosimetry of Temozolomide

Stratenwerth *et al.* | Page 1789

The specific DNA damage O^6-methylguanine induced by temozolomide was quantified and set in relation to double-strand breaks, apoptosis and senescence. The findings challenged the model of DNA damage thresholding as O^6-methylguanine induced these endpoints in glioblastoma cells without a no-effect threshold. Interestingly, senescence appears to occur at a much lower number of O^6-methylguanine molecules than cell death, indicating that low dose temozolomide impedes cytotoxicity by increasing the quiescent population. The data indicate a) need of inhibiting selectively senescence in order to ameliorate the killing effects and b) quantification of O^6-methylguanine could serve as a potential biomarker of temozolomide intratumoral dose.

TKI Resistance by KIT Low Cells in GIST

Banerjee *et al.* | Page 2035

Although imatinib can target KIT mutations in gastrointestinal stomach tumor, 40% of localized tumors recur within 5 years. In this study, Sicklick and colleagues report a population of CD34+KITlow GIST cells with a cancer stem cell-like expression profile and were enriched by imatinib treatment. Tumors with low KIT expression had activated Gas6/AXL and NF-κB pathways which could be targeted by bemcentinib (AXL inhibitor) or bardoxolone (NF-κB inhibitor) alone or in combination with imatinib. Their findings present a new population of resistant cells that can be overcome in recurrent GIST disease.

Anti-CD19 CAR T Cells Engineered to Target AML

Rennert *et al.* | Page 2071

Despite advances in experimental therapeutics for refractory acute myeloid leukemia (AML), it remains incurable. The success of CD19 CAR T cells in hematologic malignancies has led to their development in expanding indications. In this manuscript, Rennert and colleagues describe the preclinical development of a CD19-anti-CLEC12A bridge-protein secreting CAR T cell targeting CLEC12A in AML. The CAR19 cells secrete the biparatopic bridging protein to increase the cytotoxicity against CLEC12A-positive AML cells *in vitro* and *in vivo*. The efficacy of these cells demonstrates a means to thwart resistance by enhancing CD19-based CAR T cells.

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